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A straightforward synthesis of 4-substituted 3,4-dihydro-1*H*-2,1,3-benzothiadiazine 2,2-dioxides

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Substituted 3,4-dihydro-1*H*-2,1,3-benzothiadiazine 2,2-dioxides **11** have been efficiently prepared in steps from the sulfamide **9** by condensation of anion **II**, derived from **9** by metal-halogen exchange, aromatic and aliphatic aldehydes and cyclodehydration of the so-formed alcohols **10** under acidic conditions. © 2000 Elsevier Science Ltd. All rights reserved.

ords: bicyclic heterocyclic compounds; benzothiazines; lithiation; cyclization.

eterocycles incorporating a sulfamido moiety have been reported to possess a variety of interesting biological activities.¹ For example, aminothiadiazole 1,1-dioxides have shown antihypertensive and vasodilating properties.² Sedative and mild tranquilizer behaviors have also been reported for benzothiadiazine dioxides.³ Special mention should be made of bentazone (3-isopropyl-1*H*-2,1,3-benzothiadiazin-4-one 2,2-dioxide) which presents an important herbicidal activity.⁴

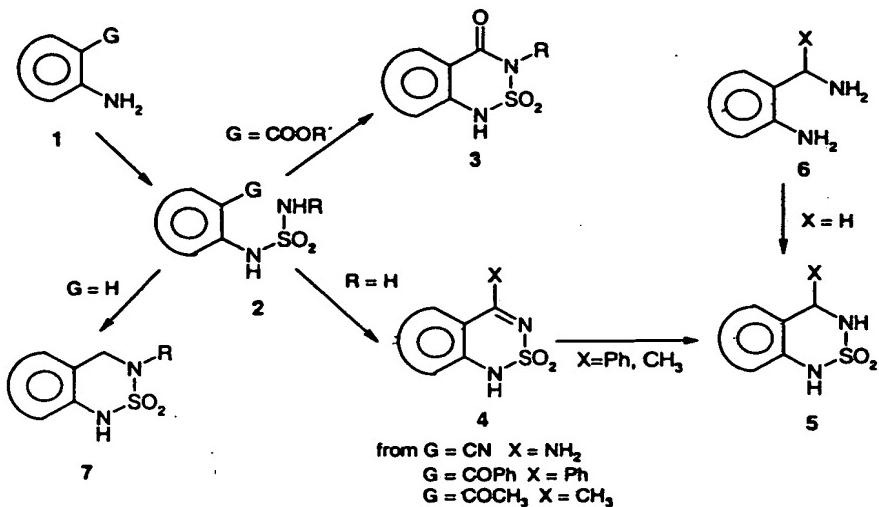
The usual procedure for the preparation of fused 1*H*-2,1,3-thiadiazine 2,2-dioxides is a one-step approach involving sulfamoylation of *ortho* substituted amino derivatives **1** followed by closure.¹ Thus, from *o*-aminobenzoates, *o*-aminobenzonitriles or 2-aminobenzophenones (*H*-oxo,⁵ 4-amino⁶ or 4-phenyl⁷ 1*H*-2,1,3-benzothiadiazines **3** or **4** have been obtained respectively (Scheme 1).

Catalytic hydrogenation of **4** (*X* = Ph, CH₃), using Adams catalyst, yielded the corresponding 4,5-dihydro derivatives **5**. These compounds can be prepared directly by reaction of 2-aminobenzenes **6** (*X* = H) with either sulfonyl chloride⁸ or sulfamide.⁹ More recently, Pews reported the synthesis of 3-alkyl derivatives **7** by reaction of *N*-alkyl-*N'*-arylsufamides **2** (*G* = H) with oxane.¹⁰ The scope of these methods is related to the substitution in the benzo moiety and so C4 position was unsubstituted in almost all cases.

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Scheme 1.

As 4-substituted 1*H*-2,1,3-benzothiadiazine 2,2-dioxides 11 were required for new drug candidate synthesis, we decided to explore a more straightforward synthetic approach. A simple retrosynthetic analysis led us to recognize that *o*-idoaniline 8 could be a suitable precursor (Fig. 1). So we decided to explore this approach by carrying out, as the key step, the condensation of the corresponding ArLi derived from 9 with aldehydes in order to get alcohols 10, which could subsequently be cyclodehydrated under acidic conditions.

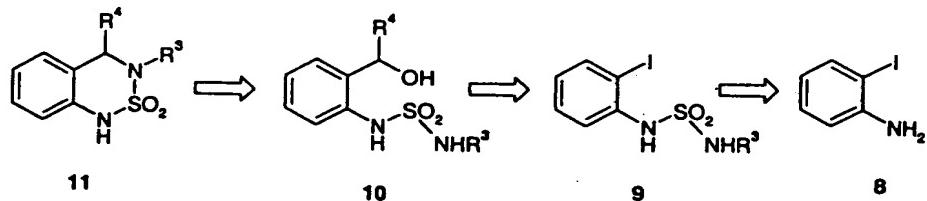
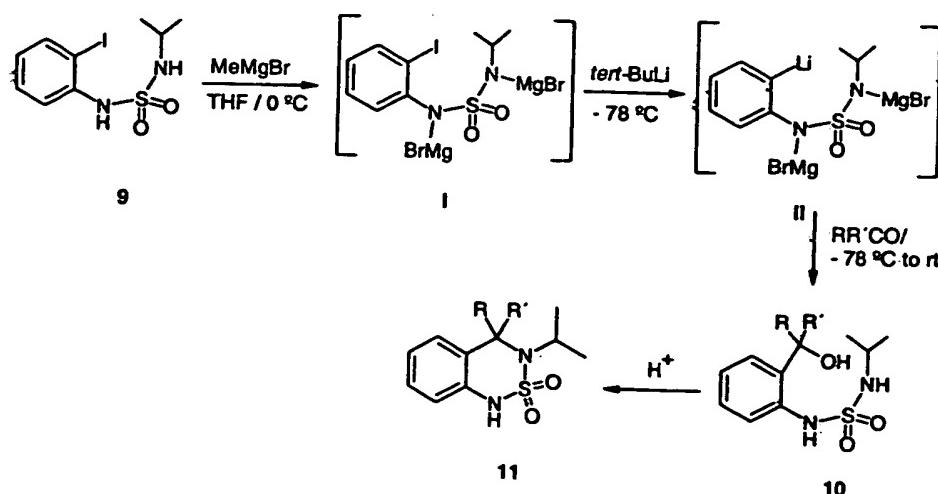


Figure 1.

In this communication, we report the successful transformation of 9 ($R^3 = i\text{-Pr}$, obtained from 8 by a standard procedure¹⁰) into 11¹¹ via this approach, thus allowing different substitution patterns at C-4.

The synthesis of 10 required the formation of the trianion II, necessitating the removal of the two acidic protons of 9 before the metal-halogen exchange. For this purpose, we chose methylmagnesium bromide, a base which would not interfere with the halogen. The deprotonation was performed at 0°C in THF until no further methane evolution was observed. For the metal-halogen exchange, *tert*-BuLi was the reagent of choice due to its high iodine affinity, even in the presence of sensitive groups.¹² The process took place at -78°C over 20 min. Finally, the addition of the electrophile gave the desired alcohol 10 (Scheme 2).

The condensation of II with aromatic and aliphatic aldehydes worked well (Table 1, entries a-g) giving 10 in good yields. The only exception was aldehyde of entry h, where the tribromoac-



Scheme 2.

hyde acted as a bromine donor, affording 12 (Fig. 2) in 70%. However, when ketones were as electrophiles (entries j-l) the condensation did not proceed, with only reduced product (g. 2) being isolated in more than 80%. In order to increase the reactivity of the ketones, BF_3 was added to the reaction but this only yielded a complex mixture of products.

Table 1
Two-step synthesis of 4-substituted 3,4-dihydro-1*H*-2,1,3-benzothiadiazine 2,2-dioxides 11

Entry	RR'CO	Yield (%)		Entry	RR'CO	Yield (%)	
		10	11			10	11
a		80	82 ^a	g		90	—
b		88	80 ^b	h		—	—
c		80	80 ^b	i		73	98 ^a
d		86	24 ^b (70) ^c	j		—	—
e		62	97 ^a	k		—	—
f	$\text{CH}_3(\text{CH}_2)_8\text{CHO}$	77	67 ^a	l		—	—

^a $\text{CH}_3\text{SO}_3\text{H}/\text{CH}_2\text{Cl}_2/1\text{h}/\text{rt}$ (except for entry e as indicated in the text). ^b $\text{CF}_3\text{CO}_2\text{H}/\text{CH}_2\text{Cl}_2/10\text{ min}/\text{rt}$. ^c Saturated ethereal solution of hydrogen chloride/ $\text{CH}_2\text{Cl}_2/10\text{ min}/-30^\circ\text{C}$.

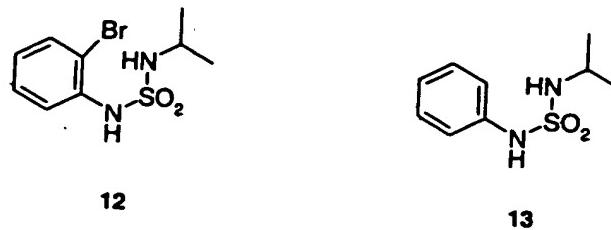


Figure 2.

The one exception was cyclobutanone (entry i), which condensed quite well to yield the expected alcohol **10i** in 73% yield. These results can be explained by the facile enolization of both cyclopentanone and acetophenone when **II** is present, while the enolate of cyclobutanone possesses high skeletal strain and so is less readily formed. In this case the enolization is not thermodynamically favored and so the reaction with **II** can occur. Furthermore, the driving force of the condensation in this case could be associated with a release of strain when cyclobutanone reacts with **II**.

The final step was the acid-catalyzed cyclodehydration of the benzylic alcohols **10**. Methanesulfonic acid was initially used, producing the expected heterocycle **11** in high yield. However, 4-pyridine carbaldehyde required more vigorous conditions (reflux temperature), probably due to the protonation of the basic nitrogen atom. For the five-membered heterocyclic aldehydes (Table 1, entries b-d), trifluoroacetic acid, a weaker acid, was used yielding the expected products in good yields in the case of the thiophene carbaldehydes and a very poor yield (24%) for the furyl derivative. The sensitivity of the furan ring toward acid media required the cyclization of **10d** to be run at low temperature (-30°C, saturated ethereal solution of hydrogen chloride) in order to obtain a reasonable (70%) yield of **11d**. Finally, in the case of alcohols **10** derived from aliphatic aldehydes (Table 1, entries f and g), the dehydration to the corresponding alkene was a competing process, this being the sole isolated product in the case of **10g** (70%), while **11f** was isolated in 67% yield, with only a 15% yield of the alkene side product.

Representative experimental procedure:

Compound 10: To a solution of the iodo derivative **9** (1.0 g, 2.94 mmol) in dry THF (30 mL) stirred at 0°C was added a 3 M solution of methyl magnesium bromide (2.15 mL, 6.47 mmol). The mixture was stirred for 1 h and then cooled to -78°C. A 1.7 M solution of *tert*-BuLi (3.8 mL, 6.47 mmol) was added and the solution stirred at this temperature for 30 min, then the carbonyl derivative (1.2 mol) was added at -78°C. The mixture was then heated to room temperature. After 1 h at this temperature, the reaction mixture was quenched with saturated ammonium chloride solution and extracted into CH₂Cl₂ (3×25 mL). The combined organic phases were dried over Na₂SO₄, filtered, and evaporated to dryness. The residue was purified by flash chromatography using hexane/EtOAc (8:2) as eluent.

Compound 11: To a solution of the benzylic alcohol **10** (1 mmol) in CH₂Cl₂ (15 mL) was added the corresponding acid (5 mmol) and the mixture was stirred as described for each case (see footnotes to Table 1). The reaction mixture was quenched with saturated NaHCO₃ solution and worked-up as indicated above for **10**. The crude mixture was purified by flash chromatography using hexane/EtOAc (8:2) as eluent. The oily product obtained crystallized as a white powder on standing with hexane.

knowledgements

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